

## PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/165826>

Please be advised that this information was generated on 2018-07-07 and may be subject to change.



## ANALYSIS

## Towards evidence based research

To avoid waste of research, no new studies should be done without a systematic review of existing evidence, argue **Hans Lund and colleagues**

Hans Lund *professor*<sup>1 2</sup>, Klara Brunnhuber *product manager*<sup>3</sup>, Carsten Juhl *associate professor*<sup>1 4</sup>, Karen Robinson *associate professor*<sup>5</sup>, Marlies Leenaars *associate professor*<sup>6</sup>, Bertil F Dorch *director*<sup>7</sup>, Gro Jamtvedt *dean*<sup>2 8</sup>, Monica W Nortvedt *dean*<sup>2</sup>, Robin Christensen *professor*<sup>9</sup>, Iain Chalmers *coordinator*<sup>10</sup>

<sup>1</sup>SEARCH Research Group, Department of Sports Sciences and Clinical Biomechanics, University of Southern Denmark, 55 DK 5230 Odense, Denmark; <sup>2</sup>Centre for Evidence-Based Practice, Bergen University College, Bergen, Norway; <sup>3</sup>Evidence Centre, BMJ, London, UK; <sup>4</sup>Department of Rehabilitation, Copenhagen University Hospital, Herlev and Gentofte, Denmark; <sup>5</sup>Johns Hopkins University, Baltimore, MD, USA; <sup>6</sup>SYRCLE, Central Animal Laboratory, Radboud University Medical Center, Nijmegen, the Netherlands; <sup>7</sup>University Library of Southern Denmark, University of Southern Denmark, Odense, Denmark; <sup>8</sup>Department for Evidence Synthesis, Norwegian Knowledge Center for the Health Services, Oslo, Norway; <sup>9</sup>Musculoskeletal Statistics Unit, Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark; <sup>10</sup>James Lind Initiative, Oxford, UK

Whether or not today's medical researchers, like Isaac Newton, see themselves as "standing on the shoulders of giants," they might still be expected to build systematically on previous research when planning new studies. Even though this issue was highlighted as early as 2005,<sup>1 2</sup> numerous studies indicate that researchers do not use a systematic methodology to identify and refer to earlier research when justifying, designing, or discussing new research.<sup>3-11</sup> This is true, even in high quality clinical studies published in the most prestigious medical journals.<sup>4-12</sup> Rather, medical researchers select studies to cite based primarily on preferences and strategic considerations.<sup>13-18</sup> The term "evidence based research" was coined in 2009 to indicate the approach that is needed to reduce this practice, which is an important source of research waste<sup>19</sup> and risks unnecessary harm for patients and study participants.

In view of the easy access to both electronic research databases and high quality systematic reviews—spearheaded by groups such as the Cochrane Collaboration, and numerous evidence synthesis centres worldwide—there is little excuse for researchers failing to refer to current systematic assessments of previous research. Nevertheless, authors seem to get away with being very selective,<sup>13 14</sup> preferentially citing studies with results that support the intervention they are evaluating.<sup>15-18</sup> Some research funders have already taken action. For example, the National Institute for Health Research in England now requires that applicants for primary research funding justify any proposed research by referencing a current systematic review of relevant existing research to show that they have taken account of the knowledge from previous studies.<sup>20</sup> However, much remains to be done.

It was against this background that a group of researchers decided to initiate an international network (EBRNetwork, <http://ebrnetwork.org>) to raise awareness of and confront this problem within health research. The network aims to reduce waste in research by promoting no new studies without systematic review of existing evidence and the efficient production, updating, and dissemination of systematic reviews.

### No new studies without systematic review of existing evidence

The methodology for systematic reviews requires predefined research questions, inclusion criteria, search methods, selection procedures, quality assessment, data extraction, and data analysis, with no relevant studies excluded without explanation and the results of each study contributing to the review's conclusions.<sup>21 22</sup> Basic scientific training for researchers must include an understanding of the need for a systematic review of the existing evidence<sup>21 23</sup> and the skills to critically assess, interpret, and use these reviews. For scientific, ethical, and economic reasons, current high quality systematic reviews need to be seen as an essential component of decisions about whether further studies are justified, the design of new studies, and the interpretation of new study results.<sup>1-24</sup>

Figure 1⇓ shows the process of evidence based research, from initial research question to the final decision to proceed using an optimal study design. The proposed process aims to support researchers, not to constrain them or pretend to provide all the answers: a systematic analysis is only one of many considerations when framing a research question. Researchers

may draw on clinical experience, innovation, and serendipity—similar to the large range of considerations during a journal's editorial review process.<sup>25</sup>

The number of published systematic reviews has increased steeply over recent years<sup>26</sup> so (in principle) researchers in most areas should be able to identify at least one relevant review. However, even if systematic reviews are available, researchers still face several challenges. For example, the identified systematic reviews may be out of date or of inadequate quality, necessitating additional work (requiring relevant skills, time, and resources) before the primary study. Alternatively, a lack of common measures and definitions in included studies may preclude a statistical synthesis of results, making it difficult to integrate new results.

Taking account of relevant ongoing studies when preparing systematic reviews and planning new studies presents a further challenge for evidence based research. Although registration of new trials has now become standard,<sup>27</sup> there has been less progress in the registration of other types of study.

## Efficient production, updating, and dissemination

Conducting systematic reviews is resource and time consuming, and many clinical researchers are not trained to do it. Integration of systematic reviews within the research context not only challenges researchers to acquire the required skills but to make sure that any attempts to accelerate the underlying processes do not impair quality. This necessitates changes to training curriculums; close collaboration between researchers and librarians, information specialists, and IT experts; and focused investment to optimise and automate the processes.

Various initiatives in recent years have started to tackle the problem. Most prominently, a series of articles dealing with how to avoid waste in research,<sup>28-34</sup> led to the REWARD (Reduce Waste and Reward Diligence) initiative (<http://researchwaste.net/>). Other important initiatives have been launched to prepare, update, and disseminate systematic reviews more efficiently, such as the Cochrane Collaboration.<sup>35</sup> The realisation that many of the tasks of preparing a systematic review could be automated led to the International Collaboration for the Automation of Systematic Reviews being established in 2015. New ways to prepare and update systematic reviews have been developed, such as “living systematic reviews”<sup>36 37</sup>. Cumulative meta-analyses and other methods have been used to identify whether new research is needed.<sup>38-41</sup> Of particular interest to researchers planning to conduct a systematic review are new user friendly software solutions (<http://systematicreviewtools.com/>). To avoid duplication of effort and ensure all reviews are published, it is now possible to register systematic reviews in PROSPERO,<sup>42</sup> with another registry dedicated to systematic reviews of animal studies (<http://www.syricle.nl/>).

## Responsibilities for evidence based research

Our evidence based research statement sets out the responsibilities of everyone involved in research (box). As shown in figure 1, the researcher's responsibility is to plan and conduct new research informed by all former and ongoing research relevant to the proposed new research. It is unnecessary to prepare a new systematic review if adequate reviews are already available. All researchers should be able to search for, critically appraise, and interpret systematic reviews in the context of new study results. Conducting or updating a

systematic review can be outsourced, although it has been suggested that all health researchers should begin their training by preparing at least one systematic review to ensure sufficient understanding.<sup>23</sup>

It is crucial that not only researchers but all other key stakeholders in the scientific process—such as patients, research funders and regulators, ethical committees, and publishers—acknowledge their responsibility for evidence based research. Research waste and unnecessary harm to patients can be prevented by granting approval only to proposals informed by a current systematic review. Demanding references to systematic reviews that synthesise all relevant earlier studies needs to become a guiding principle for all those safeguarding the research process up to publication.

Senior researchers and educators need to ensure that new researchers are taught how to conduct research that is evidence based.<sup>23</sup> Information specialists and librarians have a crucial role in teaching students to perform a systematic search for systematic reviews, and in preparing and publishing research about improved ways to perform literature searches.

Last but not least, research and adequate investment in the automation of systematic reviewing is crucial to achieve and maintain evidence based research, as the growing size of the healthcare literature and increasing complexity of studied interventions<sup>26</sup> make it impossible to keep up with the workload using traditional manual methods of reviewing.

## Invitation to action

The task of identifying and addressing the challenges for all stakeholders can only be confronted efficiently through international collaboration. The EBRNetwork has prepared a road map for publications (including a systematic review into the current status and effects of evidence based research itself) to raise awareness of the challenges for different stakeholder groups (implication papers) and to suggest how to deal with the tasks identified in or implied by the evidence based research statement (how-to papers). For more details, see [ebrnetwork.org](http://ebrnetwork.org).

We thank participants in the Bergen meeting and members of the EBRNetwork for their help in creating this statement. We are also grateful for financial support from the Research Council of Norway, Bergen University College, Norwegian Knowledge Centre for the Health Services, the Musculoskeletal Statistics Unit, the Parker Institute (supported by the Oak Foundation), and the research group SEARCH (Synthesis of Evidence and Research) at the University of Southern Denmark, for making this statement and the EBRNetwork a reality.

**Contributors and sources:** This statement arose from an inaugural meeting of the EBRNetwork in Bergen, December 2014, arranged by MWN, GJ, and HL. All authors participated in the meeting and in the development of the EBR statement.

**Competing interests:** We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare. The EBRNetwork does not accept support from health technology companies.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

- 1 Young C, Horton R. Putting clinical trials into context. *Lancet* 2005;366:107-8. doi:10.1016/S0140-6736(05)66846-8 pmid:16005318.
- 2 Chalmers I. Academia's failure to support systematic reviews. *Lancet* 2005;365:469. doi:10.1016/S0140-6736(05)70260-9 pmid:15705448.
- 3 Robinson KA, Goodman SN. A systematic examination of the citation of prior research in reports of randomized, controlled trials. *Ann Intern Med* 2011;154:50-5. doi:10.7326/0003-4819-154-1-201101040-00007 pmid:21200038.
- 4 Clarke M, Chalmers I. Discussion sections in reports of controlled trials published in general medical journals: islands in search of continents? *JAMA* 1998;280:280-2. doi:10.1001/jama.280.3.280 pmid:9676682.

## The evidence based research statement

To embark on research when there are no systematic reviews showing that a genuine uncertainty exists, particularly when the research involves people and animals, is unethical, unscientific, and wasteful. Researchers, research funders, research regulators and research ethics committees/institutional review boards, publishers of research, research institutions/educators, and information specialists often fail to use earlier research systematically when preparing to initiate, fund, or publish the results of new studies.

Below we set out stakeholders' responsibilities to meet the aims of evidence based research:

- No new studies without adequate systematic review of existing evidence showing new research is justified, and
- Efficient production, updating, and accessibility of systematic reviews

### *Aim 1: No new studies without adequate systematic review of existing evidence showing new research is justified*

#### *Researchers*

- To prioritise research questions after taking systematic account of the totality of relevant earlier research and ongoing research
- To know how to search efficiently for relevant systematic reviews and ongoing studies. If the search indicates that there are no relevant, up-to-date systematic reviews, researchers should be aware of the options for preparing or updating the review needed
- To be able to assess the risk of bias in systematic reviews
- To be able to supervise students studying for higher degrees in using and preparing systematic reviews

#### *Funding agencies*

- To evaluate whether applicants for funds have used systematic reviews of prior research to identify and help to prioritise research questions or agendas
- To evaluate whether applicants have demonstrated adequate support for their proposed research by reference to systematic reviews of prior research
- To evaluate whether the designs of proposed new studies have been informed by systematic reviews of prior research

#### *Research regulators, including research ethics committees/institutional review boards*

- To evaluate whether applicants have shown adequate support for their research questions by reference to systematic reviews of prior research. This expectation extends beyond randomised trials
- To evaluate whether the designs of proposed new studies have been informed by reference to systematic reviews of prior research

#### *Editors and reviewers*

- To assess whether the rationale and design of studies are adequately described within the context of systematic reviews of prior research
- To evaluate whether description of earlier research is sufficient to enable interpretation of the results of submitted studies within the totality of relevant evidence
- To evaluate whether proposals for further research take account of earlier and ongoing research
- To evaluate whether proposals for further research include clear descriptions of target populations, interventions, comparisons, outcome measures, and study types

#### *Educators*

- To teach the importance of an unbiased approach to knowledge synthesis (systematic review)
- To teach how to seek or prepare and use systematic reviews when planning and interpreting additional research

#### *Patients and consumers*

- Before agreeing to participate in research, patients should demand that research projects have been informed by systematic review of what is already known

### *Aim 2: Efficient production, updating, and accessibility of systematic reviews*

#### *Systematic review specialists*

- To participate in research and developmental activities to:
  - a. Improve the preparation and updating of systematic reviews
  - b. Develop automation of the preparation of systematic reviews
  - c. Develop tools for preparing systematic reviews more efficiently

#### *Information specialists and librarians*

- To help develop methods to increase the quality and currency of literature searches
- To participate in teaching researchers how to perform high quality searches for relevant studies
- To participate in research and developmental activities to:
  - a. Improve the production and updating of systematic reviews
  - b. Develop automation of the preparation of systematic reviews
  - c. Develop tools for preparing systematic reviews more efficiently

#### *Information technologists, programmers, and artificial intelligence engineers*

- To participate in research and developmental activities to:
  - a. Improve the production and updating of systematic reviews
  - b. Develop automation of the preparation of systematic reviews
  - c. Develop tools for preparing systematic reviews more efficiently

#### *Funding agencies*

- To support development and research to:
  - a. Improve the production and updating of systematic reviews
  - b. Develop automation of the preparation of systematic reviews
  - c. Develop tools for preparing systematic reviews more efficiently

#### *Recommendations*

- Instructions for authors should include requirements for evidence justifying the research for which publication is sought
- Systematic reviews should be recognised as research in their own right, comparable with other types of research activity
- A clear definition of a high quality systematic review should be prepared, agreed, and promoted

5 Clarke M, Alderson P, Chalmers I. Discussion sections in reports of controlled trials published in general medical journals. *JAMA* 2002;287:2799-801. doi:10.1001/jama.287.21.2799 pmid:12038916.

6 Cooper NJ, Jones DR, Sutton AJ. The use of systematic reviews when designing studies. *Clin Trials* 2005;2:260-4. doi:10.1191/1740774505cn090oa pmid:16279149.

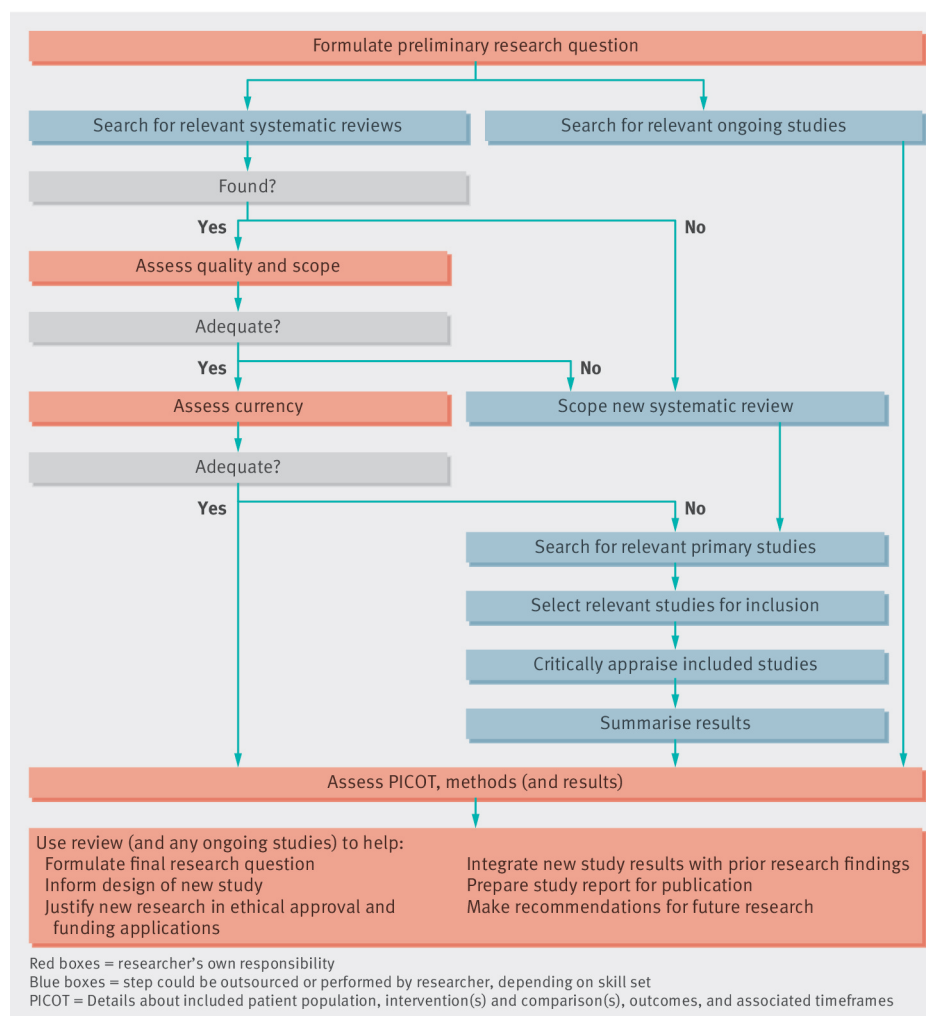
## Key messages

- Embarking on research without reviewing systematically what is already known, particularly when the research involves people or animals, is unethical, unscientific, and wasteful
- A systematic review of relevant evidence can establish whether the proposed research is truly needed
- Some research funders now require applicants to refer to a systematic review of existing research
- Research waste can also be reduced by efficient production, updating, and dissemination of systematic reviews

- 7 Fergusson D, Glass KC, Hutton B, Shapiro S. Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding? *Clin Trials* 2005;2:218-29, discussion 229-32. doi:10.1191/1740774505cn085oa pmid:16279145.
- 8 Clarke M, Hopewell S, Chalmers I. Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting. *Lancet* 2010;376:20-1. doi:10.1016/S0140-6736(10)61045-8 pmid:20609983.
- 9 Sheth U, Simunovic N, Torretta P 3rd, Einhorn TA, Bhandari M. Poor citation of prior evidence in hip fracture trials. *J Bone Joint Surg Am* 2011;93:2079-86. doi:10.2106/JBJS.J.01274 pmid:22262379.
- 10 Habre C, Tramèr MR, Pöpping DM, Elia N. Ability of a meta-analysis to prevent redundant research: systematic review of studies on pain from propofol injection. *BMJ* 2014;348:g5219. doi:10.1136/bmj.g5219 pmid:25161280.
- 11 Sawin VI, Robinson KA. Biased and inadequate citation of prior research in reports of cardiovascular trials is a continuing source of waste in research. *J Clin Epidemiol* 2016;69:174-8. pmid:26086727.
- 12 Clarke M, Hopewell S, Chalmers I. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. *J R Soc Med* 2007;100:187-90. doi:10.1258/jrsm.100.4.187 pmid:17404342.
- 13 Greenberg SA. How citation distortions create unfounded authority: analysis of a citation network. *BMJ* 2009;339:b2680. doi:10.1136/bmj.b2680 pmid:19622839.
- 14 Bastiaansen JA, de Vries YA, Munafo MR. Citation distortions in the literature on the serotonin-transporter-linked polymorphic region and amygdala activation. *Biol Psychiatry* 2015;78:e35-6. doi:10.1016/j.biopsych.2014.12.007 pmid:25866295.
- 15 Thornley C, Watkinson A, Nicholas D, et al. The role of trust and authority in the citation behaviour of researchers. *Information Research* 2015;20: 677.
- 16 Perino AC, Hoang DD, Holmes TH, et al. Association between success rate and citation count of studies of radiofrequency catheter ablation for atrial fibrillation: possible evidence of citation bias. *Circ Cardiovasc Qual Outcomes* 2014;7:687-92. doi:10.1161/CIRCOUTCOMES.114.000912 pmid:25205786.
- 17 Jannot AS, Agoritsas T, Gayet-Ageron A, Perneger TV. Citation bias favoring statistically significant studies was present in medical research. *J Clin Epidemiol* 2013;66:296-301. doi:10.1016/j.jclinepi.2012.09.015 pmid:23347853.
- 18 Fiorentino F, Vasilakis C, Treasure T. Clinical reports of pulmonary metastasectomy for colorectal cancer: a citation network analysis. *Br J Cancer* 2011;104:1085-97. doi:10.1038/sj.bjc.6606060 pmid:21386844.
- 19 Robinson KA. Use of prior research in the justification and interpretation of clinical trials. Johns Hopkins University, 2009.
- 20 National Institute for Health Research. Guidance notes for applicants: outline applications. NIHR, 2016.
- 21 Chalmers I. The lethal consequences of failing to make full use of all relevant evidence about the effects of medical treatments: the importance of systematic reviews. In: Rothwell PM, ed. *Treating individuals—from randomised trials to personalised medicine*. Lancet, 2007: 37-58.
- 22 Lund H, Juhl C, Christensen R. Systematic reviews and research waste. *Lancet* 2016;387:123-4. doi:10.1016/S0140-6736(15)01354-9 pmid:26841992.
- 23 Mahtani KR. All health researchers should begin their training by preparing at least one systematic review. *J R Soc Med* 2016;109:264-8. doi:10.1177/0141076816643954 pmid:27118697.
- 24 Kleinert S, Benham L, Collingridge D, Summerskill W, Horton R. Further emphasis on research in context. *Lancet* 2014;384:2176-7. doi:10.1016/S0140-6736(14)62047-X pmid:25625383.
- 25 Jefferson T, Deeks J. The use of systematic reviews for editorial peer reviewing: a population approach. In: Godlee F, Jefferson T, eds. *Peer review in health sciences*. BMJ Books, 1999: 224-34.
- 26 Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? *PLoS Med* 2010;7:e1000326. doi:10.1371/journal.pmed.1000326 pmid:20877712.
- 27 Dickersin K, Rennie D. Registering clinical trials. *JAMA* 2003;290:516-23. doi:10.1001/jama.290.4.516 pmid:12876095.
- 28 Chalmers I, Glasziou P. Systematic reviews and research waste. *Lancet* 2016;387:122-3. doi:10.1016/S0140-6736(15)01353-7 pmid:26841991.
- 29 Macleod MR, Michie S, Roberts I, et al. Biomedical research: increasing value, reducing waste. *Lancet* 2014;383:101-4. doi:10.1016/S0140-6736(13)62329-6 pmid:24411643.
- 30 Ioannidis JP, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014;383:166-75. doi:10.1016/S0140-6736(13)62227-8 pmid:24411645.
- 31 Glasziou P, Altman DG, Bossuyt P, et al. Reducing waste from incomplete or unusable reports of biomedical research. *Lancet* 2014;383:267-76. doi:10.1016/S0140-6736(13)62228-X pmid:24411647.
- 32 Chan AW, Song F, Vickers A, et al. Increasing value and reducing waste: addressing inaccessible research. *Lancet* 2014;383:257-66. doi:10.1016/S0140-6736(13)62296-5 pmid:24411650.
- 33 Al-Shahi Salman R, Beller E, Kagan J, et al. Increasing value and reducing waste in biomedical research regulation and management. *Lancet* 2014;383:176-85. doi:10.1016/S0140-6736(13)62297-7 pmid:24411646.
- 34 Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet* 2009;374:86-9. doi:10.1016/S0140-6736(09)60329-9 pmid:19525005.
- 35 Starr M, Chalmers I, Clarke M, Oxman AD. The origins, evolution, and future of The Cochrane Database of Systematic Reviews. *Int J Technol Assess Health Care* 2009;25(Suppl 1):182-95. doi:10.1017/S026646230909062X pmid:19534840.
- 36 Elliott JH, Turner T, Clavisi O, et al. Living systematic reviews: an emerging opportunity to narrow the evidence-practice gap. *PLoS Med* 2014;11:e1001603. doi:10.1371/journal.pmed.1001603 pmid:24558353.
- 37 Vandvik PO, Brignardello-Petersen R, Guyatt GH. Living cumulative network meta-analysis to reduce waste in research: A paradigm shift for systematic reviews? *BMC Med* 2016;14:59. doi:10.1186/s12916-016-0596-4 pmid:27025849.
- 38 Clarke M, Brice A, Chalmers I. Accumulating research: a systematic account of how cumulative meta-analyses would have provided knowledge, improved health, reduced harm and saved resources. *PLoS One* 2014;9:e102670. doi:10.1371/journal.pone.0102670 pmid:25068257.
- 39 Siebert U, Rochau U, Claxton K. When is enough evidence enough? - Using systematic decision analysis and value-of-information analysis to determine the need for further evidence. *Z Evid Fortbild Qual Gesundheitsw* 2013;107:575-84. doi:10.1016/j.zefq.2013.10.020 pmid:24315327.
- 40 Garner P, Hopewell S, Chandler J, et al. Panel for updating guidance for systematic reviews (PUGs). When and how to update systematic reviews: consensus and checklist. *BMJ* 2016;354:i3507. doi:10.1136/bmj.i3507 pmid:27443385.
- 41 Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008;61:64-75. doi:10.1016/j.jclinepi.2007.03.013 pmid:18083463.
- 42 Booth A, Clarke M, Dooley G, et al. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. *Syst Rev* 2012;1:2. doi:10.1186/2046-4053-1-2 pmid:22587842.

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>

## Figure



**Fig 1** Flow chart for evidence based research